Versatile Construction of 6-Substituted *cis*-2,8-Dioxabicyclo[3.3.0]octan-3-ones. Short Enantioselective Total Syntheses of Cheloviolenes A and B and Dendrillolide C

Yuriy Slutskyy,[†, ξ] Christopher R. Jamison,[†, ξ] Peng Zhao,[†] Juyeol Lee,[†] Young Ho Rhee,[‡] Larry E. Overman[†,*]

[†] *Department of Chemistry, University of California, Irvine, California 92697-2025*

[‡] *Department of Chemistry, Pohang University of Science and Technology, Hyoja-dong San 31, Pohang, Kyungbook, Republic of Korea 790-784*

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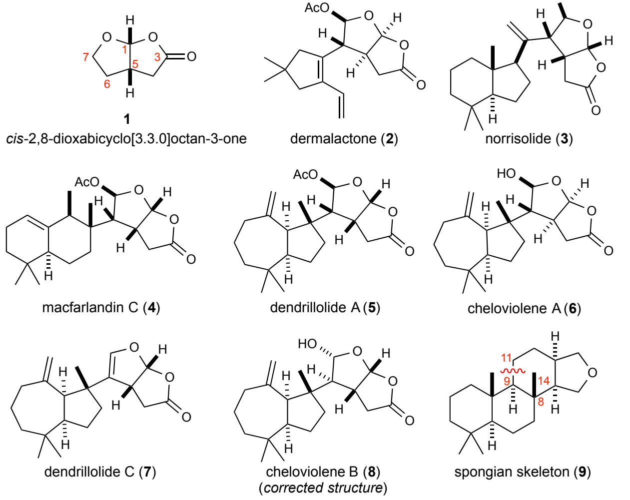
ABSTRACT: A short enantioselective synthesis of 6-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones is described. The pivotal step is coupling of a tertiary radical generated directly from a tertiary alcohol with a 3-chloro-5-alkoxybutenolide. This strategy is applied towards scalable 14–15 step syntheses of three rearranged spongian diterpenoids, cheloviolenes A and B and dendrillolide C.

The *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one (**1**) ring system is found in nearly 100 natural products (Figure 1).[1] In a subset of these, the dioxabicyclic ring is isolated and joined at C-6 to a hydrocarbon fragment of nine or fourteen carbons. The fungal sesquiterpenoid **2** is an example of the former group,[2] whereas diterpenoids **3**–**8** exemplify the larger group that were isolated from marine sponges or nudibranchs.[3] Norrisolide (**3**) was the first of these natural products to be described.[4] In the more common members of this group, the dioxabicyclo[3.3.0]octan-3-one fragment is attached to a quaternary carbon of the hydrocarbon unit, for example diterpenoids **4**–**8**. Two distinct structural subtypes that differ in whether the hydrocarbon fragment resides on the concave or convex face of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragment, exemplified respectively by dendrillolide A (**5**)[5] and cheloviolene A (**6**),[6] are observed.[7] The relative configurations of norrisolide (**3**), macfarlandin C (**4**) and cheloviolene A (**6**) are known by virtue of single-crystal X-ray analyses.[4,6,8] The absolute configuration of norrisolide (**3**) was established by Thedorakis' inaugural total synthesis,[9] whereas that of rearranged spongian diterpenoids **4**–**8** and structurally related natural products has not been established. They are suggested to be as depicted in Figure 1 by virtue of their presumed biosynthesis from precursors having a spongian skeleton (**9**).[3,10]



1
cis-2,8-dioxabicyclo[3.3.0]octan-3-one

dermalactone (**2**)

norrisolide (**3**)

macfarlandin C (**4**)

dendrillolide A (**5**)

cheloviolene A (**6**)

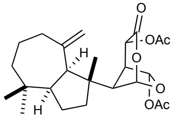
dendrillolide C (**7**)

cheloviolene B (**8**)
(*corrected structure*)

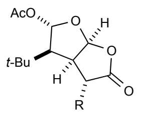
spongian skeleton (**9**)

Figure 1. Terpenoids containing isolated *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragments and the presumed biosynthetic precursor **9** of the marine diterpenoids **3**–**8**.

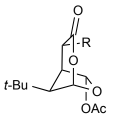
The biological activity of rearranged spongian diterpenoids of marine origin remains largely unexplored.[8,11] The unique effects on the structure of the Golgi apparatus induced by norrisolide (**3**), macfarlandin E (**10**), and structurally simplified racemic analogs containing a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one (**11**) or 2,7-dioxabicyclo[3.2.1]octan-3-one ring (**12**) are of most significance.[12,13] The consequences of exposing the Golgi to norrisolide (**3**), or macfarlandin E (**10**) and dioxabicyclo[3.3.0]octanones **11**–**12**, are remarkably different. Although both natural products block protein transport from the Golgi to the plasma membrane, norrisolide (**3**) induces irreversible fragmentation and delocalization of Golgi membranes throughout the cytosol in human cell lines, whereas macfarlandin E (**10**) and analogs **11**–**12** (R = OAc) induce an irreversible Golgi organization phenotype that is characterized by the formation of small fragments that remain in the pericentriolar region. In addition, we have shown that macfarlandin E and analogs **11**–**12** react with primary amines, including lysine side chains of the enzyme lysozyme, to form pyrroles, a conjugation that potentially could be important for the observed effects of these agents on the Golgi.[13b]



macfarlandin E (**10**)



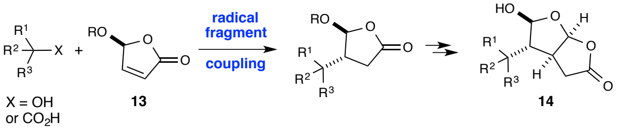
11 (R = H or OAc)



12 (R = H or OAc)

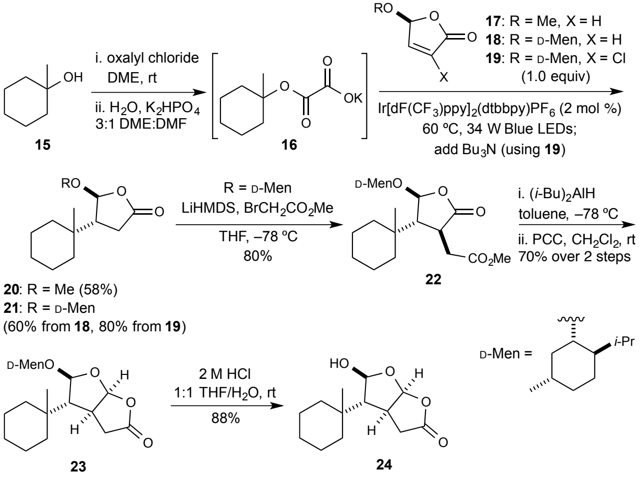
As analogs **11** and **12** appear to form identical 1,4-dialdehyde intermediates upon acetate cleavage, and structures harboring the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one ring of the former are expected to be more readily available by chemical synthesis, our studies in this area have focused recently on developing a short and versatile route to 6-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones. The sequence outlined in Scheme 1, whose pivotal step would be the coupling of a tertiary radical generated from a carboxylic acid or alcohol precursor with a 5-alkoxybutenolide (**13**), could potentially access a wide variety of dioxabicyclooctanones **14** in 5 steps, representing a significant improvement on an earlier synthesis of **11** (R = H) that required 14 steps.[13b] Moreover, the sequence proposed in Scheme 1 could provide products **14** in enantiopure form, as both enantiomers of several 5-alkoxybutenolides are commercially available.[14] We report herein the successful development of the strategy adumbrated in Scheme 1 and illustrate its utility by notably short and enantioselective total syntheses of the rearranged spongian diterpenoids **6**–**8**.

Scheme 1. General Route to 6-Substituted *cis*-2,8-Dioxabicyclo[3.3.0]octan-3-ones (14).



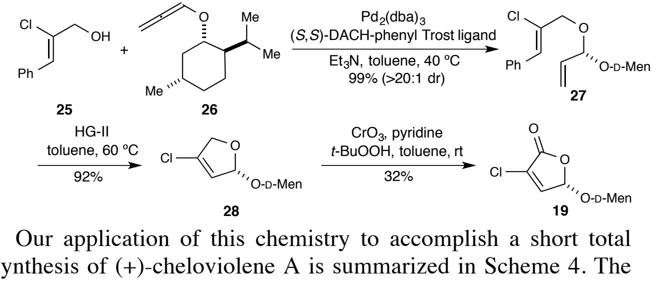
We chose 1-methylcyclohexanol (**15**) as the starting material to explore the proposed approach in the alcohol series.[15] Our initial aim was to develop a one-pot sequence for directly transforming a tertiary alcohol to a coupled product. We eventually found that exposure of alcohol **15** to 1 equiv of oxalyl chloride at room temperature in DME, followed by adding water and 3 equiv of K_2HPO_4 generated the potassium hemioxalate intermediate **16**.[16] Addition of 1 equiv of 5-methoxybutenolide **17**,[17] followed by photoredox-catalyzed coupling as described previously[16] provided **20** as a single stereoisomer in 58% yield. Using the analogous menthyloxy butenolide **18**,[18] coupled product **21** was again generated as a single stereoisomer in 60% yield. As we had previously observed high yields in the coupling of a tertiary radical with an α-chlorocyclopentenone,[19] we turned to examine chlorobutenolide **19** as the radical acceptor. In this case, addition of the tertiary radical to the more activated acceptor was significantly more efficient. Following the initial fragment coupling, simply adding 10 equiv of tri-*n*-butylamine to the reaction mixture and allowing the subsequent photocatalytic dechlorination to proceed for 4 h gave **21** in 80% yield from alcohol **15**.[20] The coupled product **21** could be transformed in 49% yield over four steps to the 6-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one **24** by way of isolated intermediates **22** and **23**.

Scheme 2. Optimization of the Fragment Coupling Step and Elaboration of the Coupled Product to the 6-Substituted *cis*-2,8-Dioxabicyclo[3.3.0]octan-3-one 24.



Enantiopure 3-chloro-5-alkoxybutenolide **19** was available by the sequence outlined in Scheme 3.[21] Palladium-catalyzed enantioselective hydroalkoxylation of D-menthol-derived allene **26** with allylic alcohol **25** by the general method of Rhee[22] delivered acetal **27** in 99% yield as a single detectable diastereomer (by ^{1}H NMR analysis). Using the Hoveyda-Grubbs second-generation catalyst, ring-closing metathesis of **27** gave dihydrofuran **28** in excellent yield on gram-scale.[23] Allylic oxidation of **28** to yield the corresponding butenolide not surprisingly was extremely challenging. Under the best conditions defined to date,[24] butenolide **19** was formed in 32% yield. The opposite enantiomer of butenolide **19** was readily accessible on gram-scale by the same sequence, starting from L-menthol and utilizing the *R*,*R* enantiomer of the Trost ligand.[25]

Scheme 3. Synthesis of Enantiopure 3-Chloro-5-Alkoxybutenolide 19.



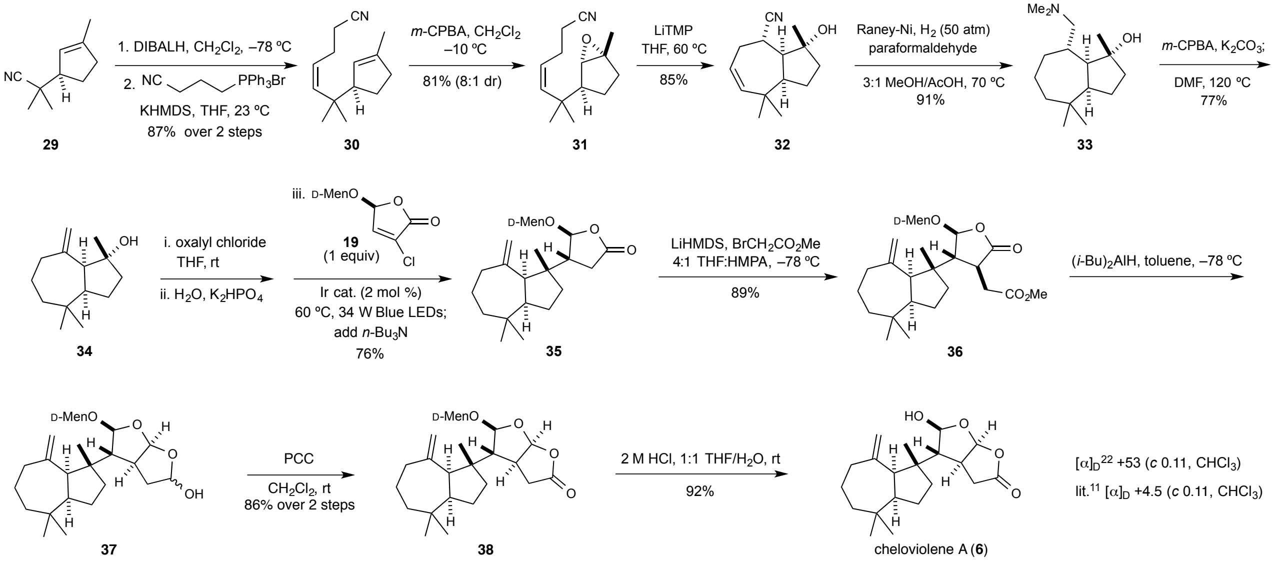
Our application of this chemistry to accomplish a short total synthesis of (+)-cheloviolene A is summarized in Scheme 4. The synthesis began with the known cyclopentene nitrile **29**,[26] which is accessible from (+)-fenchone as a single alkene regioisomer in three steps by a sequence we optimized to provide **29** on ~10 g scale.[27] Reduction of **29** with $(i\text{-Bu})_2AlH$ and Wittig elaboration of the resulting aldehyde provided dienyl nitrile **30** in 87% yield over two steps. The trisubstituted double bond of this intermediate was regioselectively epoxidized upon reaction with *m*-chloroperbenzoic acid (*m*-CPBA) at –10 °C to give an 8:1 mixture of stereoisomers from which epoxide **31** was isolated in 81% yield after chromatographic purification. Deprotonation of **31** with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) induced stereospecific Stork epoxy/nitrile cyclization, to form *cis*-perhydrazulene alcohol **32** in 85% yield.[28] To our knowledge, this is the first example of forming a seven-membered ring in this way.[29] After examining several alternatives, the elaboration of the nitrile to an exocyclic methylene was best realized in a classical fashion. First, global reduction with concomitant Eschweiler-Clarke methylation yielded tertiary amine **33**. After treatment with *m*-CPBA, the resulting amine oxide underwent clean Cope elimination when heated in DMF at 120 °C to yield alcohol **34** in 70% yield over the two steps. This six-step sequence provided convenient access to *cis*-perhydrazulene alcohol **34** on gram-scale.

Our early survey of conditions for carrying out the pivotal coupling reaction of the tertiary radical derived from alcohol **34** and butenolides **17** and **19** indicated that ethereal solvents (THF or DME) were optimal. In addition, these exploratory investigations showed that a significant competing reaction was reduction of the initially generated tertiary radical. Thus, the yield of the coupled product was enhanced when the concentration of the reaction was increased from 0.05 M to 0.6 M in THF. Under optimal conditions, the one-step generation of the potassium hemioxalate salt from **34** and the photoredox catalyzed coupling of the derived radical with 1 equiv of butenolide **19** was highly efficient, providing product **35** in 76% yield after addition of tri-*n*-butylamine.

Elaboration of coupled product **35** to (+)-cheloviolene A (**6**) began with alkylation of the lactone enolate with methyl bromoacetate to deliver ester **36** as a single stereoisomer. Reduction of **36** with 2.2 equiv of $(i\text{-Bu})_2AlH$ in toluene at –78 °C gave rise to an inconsequential mixture of dioxabicyclo[3.3.0]octane lactol epimers **37**. The crude mixture of lactols was oxidized to the corresponding lactone **38** upon treatment with PCC. Finally, subjecting dioxabicyclooctanone **38** to dilute HCl provided (+)-cheloviolene A (**6**) in 79% overall yield from ester **36**. Synthetic crystalline **6** exhibits a different optical rotation from the one reported in literature, synthetic: $[\alpha]_D^{22}$ +53 (*c* 0.11, $CHCl_3$), literature: $[\alpha]_D$ +4.5 (*c* 0.11, $CHCl_3$).[11] However, the spectroscopic data and the melting point for synthetic **6** compared well with those reported for the natural product isolated from the New Zealand sponge *Chelonaplysilla violacea*, leaving little doubt as to their identity.[6,27,30]

The key coupling step of an identical sequence to synthesize the diastereomeric tetracyclic product **8** is summarized in Scheme 5. The slightly lower yield in the fragment coupling step (68%) likely reflects a slight miss match in the addition of the tertiary radical generated from alcohol **34** to butenolide **39**. The relative configuration of synthetic **8** was confirmed by single-crystal X-ray analysis.[27] Structure **8** originally had been assigned erroneously to a diterpenoid isolated from a *Chelonaplysilla* sp. sponge found in Palau and referred to as chelonoplysin B. This Palaun marine isolate was shown later to be identical to cheloviolene A (**6**).[6b] ^{1}H and ^{13}C NMR data for synthetic **8** were nearly identical to those reported for cheloviolene B, which had been isolated together with cheviolene A (**6**) and assigned on the basis of NMR data to be the lactol epimer of **6**. This original assignment is incorrect and the structure of cheloviolene B should be revised to **8**.

Scheme 4. Short Total Synthesis of (+)-Cheloviolene A (6) from (+)-Fenchone-Derived Cyclopentene Nitrile 29.

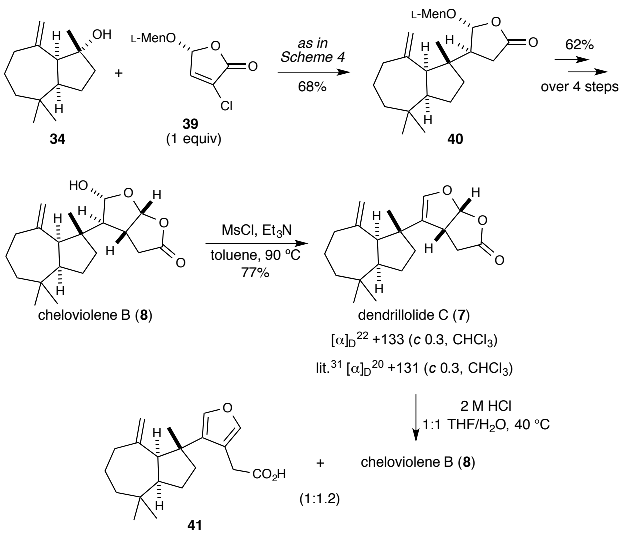


$[\alpha]_D^{22}$ +53 (*c* 0.11, $CHCl_3$)

lit.[11] $[\alpha]_D$ +4.5 (*c* 0.11, $CHCl_3$)

The synthesis of dendrillolide C (**7**) and its interconversion with cheloviolene B (**8**) is summarized in Scheme 5. Reaction of **8** with 2.5 equiv of MsCl and excess Et_3N in toluene at 90 °C provided (+)-dendrillolide C (**7**) in 77% yield. ^1H NMR data of synthetic **7** were indistinguishable from that reported for the diterpenoid isolated from the sponge *Dendrilla* sp. collected in Palau.[27,31] As the relative configuration of the stereogenic carbons that join the two rings of cheloviolene B (**8**) are opposite to that found in diterpenoids **4**–**6** and are opposite to that of the C-8 and C-14 stereocenters of a spongian precursor, Faulkner had suggested that structure **8** might arise by hydration of the enol ether functionality of dendrillolide C (**7**).[11] To test this hypothesis, synthetic dendrillolide C (**7**) was treated with various aqueous acids. Although it was stable to 2 M HCl in 1:1 THF/H_2O at room temperatuere, at 40 °C a 1.2:1 mixture of cheloviolene B (**8**) and furan **41** was formed.[32]

Scheme 5. Total Syntheses of (+)-Cheloviolene B (8) and (+)-Dendrillolide C (7), and Stereoselective Hydration of Dendrillolide C to Form Cheloviolene B.



$[\alpha]_D^{22}$ +133 (*c* 0.3, $CHCl_3$)

lit.[31] $[\alpha]_D^{20}$ +131 (*c* 0.3, $CHCl_3$)

In summary, a five-step enantioselective sequence to prepare 6-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones has been developed. High-yielding fragment coupling of a tertiary radical generated directly from a tertiary alcohol with an enantiopure 3-chloro-5-alkoxybutenolide in which both precursors are used in equimolar amounts is the pivotal step of this synthetic strategy. This sequence was exemplified by short syntheses of (+)-cheloviolenes A and B and (+)-dendrillolide C, which established the absolute configuration of these diterpenoid natural products and corrected the structural assignment for cheloviolene B. This rapid and versatile construction of the 6-substituted-*cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones should aid in future studies of biological activity of molecules harboring this ring system.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and CIF files for X-ray structures of compounds **8** and **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

leoverma@uci.edu

Author Contributions

ξY.S. and C.R.J. contributed equally.

Notes

The authors declare no competing financial interest.

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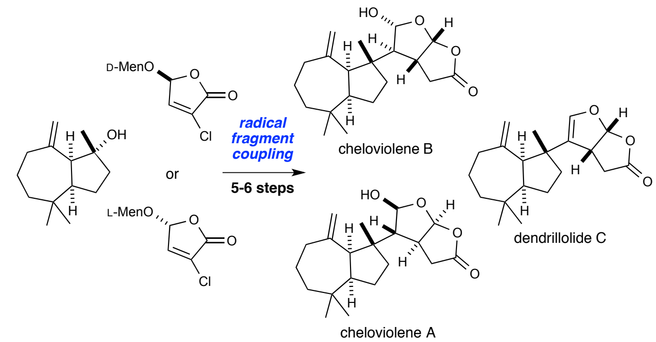

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